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LETTERS TO THE EDITOR

RE: "ESTIMATES OF THE ANNUAL NUMBER OF CLINICALLY RECOGNIZED PREGNANCIES IN THE UNITED STATES, 1981–1991"

We were pleased to see the recent *Journal* article by Saraiya et al. (1), in which the authors attempted to estimate the number of clinically recognized pregnancies that occur annually in the United States. Because pregnancies ending in live birth are determined easily from state vital statistics, this task reduces to estimating the number that end in some form of fetal loss. Because many forms of fetal loss are not routinely reported, the authors had to rely on innovative uses of sample studies to derive their numbers.

To derive the number of spontaneous abortions, they used data from the well-known Wilcox et al. study (2) based on the menstrual cycles of a large number of young women followed up over many years. From this study, Saraiya et al. (1) extracted age-specific rates of spontaneous abortion, applying them to the assumed maternal age distribution in the United States during an 11-year study period, 1981–1991.

The Wilcox et al. study (2), however, occurred 10–50 years before the Saraiya et al. (1) time period of interest. Spontaneous abortion rates may well have changed. More important, the Wilcox et al. study occurred well before the legalization of induced abortion, when the pressure from this competing pregnancy outcome was slight. In addition, the Wilcox et al. study population included only a single social class of White, college-educated women and their offspring. Despite these limitations and others (3), the Wilcox et al. study was the only one available to Saraiya et al. that provided spontaneous abortion rates by maternal age.

To update and/or confirm the Wilcox et al. study's (2) age-specific rates and therefore the Saraiya et al. study's (1) extrapolations of them, we reanalyzed data from a previous investigation (4). Our investigation was conducted within the Saraiya et al. study period; featured a multiracial, working class population; and included induced abortion as a likely pregnancy outcome (table 1). In our investigation, we followed a large cohort of pregnancies from the time of an initial pregnancy test (at gestational week 5 and beyond) until pregnancy outcome. We used fetal life table methodology to calculate the incidence of spontaneous abortion, excluding ectopic pregnancy and treating induced abortion as a censoring event.

The good news is that we were able to confirm two of the assumptions made by Saraiya et al. (1). First, we found that the incidence of spontaneous abortion increased with maternal age by roughly the same degree as found in the Wilcox et al. (2) study. Second, we found little discernible difference in spontaneous abortion rates by maternal race (table 2).

Our overall incidence of spontaneous abortion, however, was lower than that of the Wilcox et al. study (2), 0.11 versus 0.16 (0.14 in the Saraiya et al. study (1) was due to age adjustment of the Wilcox et al. rates). Our lower incidence could have resulted from lower underlying population risks, different time periods of investigation, or different measuring abilities. (Note that our 0.11 incidence excludes the first week after the missed menses; that is, it begins at 5 completed weeks from the last menstrual period and goes approximately through 20 weeks of fetal development.)

In any case, we suggest that the Saraiya et al. study (1) estimates are high even if our more recent data are not considered. Spontaneous abortion rates from the Wilcox et al. study (2), calculated in the absence of induced abortion, need to be adjusted downward in the Saraiya et al. study in the presence of induced abortion as a substantial, competing risk (5–7) (table 3). Without an adjustment, the estimated number of spontaneous abortions may be inflated by as much as 1 million.

TABLE 1. Study characteristics and percentage distribution of pregnant population, by maternal age and race, in three studies

	Study (reference no.)		
	Wilcox et al. (2)	Goldhaber and Fireman (4)	Saraiya et al. (1)*
Study type	Menstrual cohort	Left-censored pregnancy cohort	Cross-sectional, all US pregnancies
No. of pregnancies	3,901	9,055	67,453,135
Study years	1935–1970	1981–1982	1981–1991
Maternal age (years)			
<30	60.5	72.9	73.8
30–34	26.7	19.5	19.1
≥35	12.8	7.6	7.1
Maternal race			
White	100.0†	79.0	80.1
Black	0.0	6.3	16.0
Other	0.0	14.7	3.9

* Age and race distributions are based on US birth certificate data.
† Virtually all White.

TABLE 2. Incidence* of spontaneous abortion in three studies, by maternal age and race, calculated in the absence of induced abortion as a substantial competing risk

	Study (reference no.)		
	Wilcox et al. (2)	Goldhaber and Fireman (4)	Saraiya et al. (1)†
Overall	0.16	0.11	0.14
Maternal age (years)			
<30	0.11	0.09	0.11
30–34	0.18	0.12	0.18
≥35	0.28	0.26	0.28
Maternal race‡			
White	0.16	0.11	0.14
Black		0.10	0.14
Other		0.12	

* Number of spontaneous abortions divided by number of livebirths plus stillbirths plus spontaneous abortions, calculated in the absence of induced abortion as a substantial competing risk.

† Age-specific rates from the Wilcox et al. study were applied to the maternal age distribution of the United States, 1981–1991, shown in table 1.

‡ Race categories are not applicable to the Wilcox et al. study. No difference in rates by race is assumed in the Saraiya et al. study (except as driven by maternal age). Race missing for induced abortion cases in the Goldhaber and Fireman study, resulting in overestimation of spontaneous abortion risk in each race group by about 1% because of loss of denominator data.

TABLE 3. Pregnancy outcome in three studies (percentage distribution)

	Study (reference no.)		
	Wilcox et al. (2)	Goldhaber and Fireman (4)	Saraiya et al. (1)*
Livebirth plus stillbirth†	82.7	70.9	63.0
Induced abortion	1.4	18.9	21.9
Spontaneous abortion	15.5	9.2	13.8
Ectopic pregnancy	0.4	1.0	1.3

* Assumed age-specific rates of spontaneous abortion in the Wilcox et al. study.

† Stillbirth refers to fetal losses after 20 weeks of gestation as reported on fetal death certificates.

The magnitude of the risk of spontaneous abortion has been, and remains, elusive. Recent prospective investigations that follow early pregnancy by measuring maternal human chorionic gonadotropin show that incidences of spontaneous abortion in the clinical period (after 4 completed weeks from the last menstrual period), in the absence of induced abortion as a competing risk, range from 10 to 18 percent (8–12). Between-studies differences are at least partially attributed to difficulties in distinguishing between categories of *occult* and *clinical* pregnancies around the time of the missed menses (11).

References

1. Saraiya M, Berg CJ, Shulman H, et al. Estimates of the annual number of clinically recognized pregnancies in the United States, 1981–1991. Am J Epidemiol 1999;149:1025–9.
2. Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. Am J Epidemiol 1981;114:548–53.
3. Wilcox AJ, Gladen BC. Spontaneous abortion: the role of heterogeneous risk and selective fertility. Early Hum Dev 1982;7:165–78.
4. Goldhaber MK, Fireman BH. The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. Epidemiology 1991;2:33–9.
5. Susser E. Spontaneous abortion and induced abortion: an adjustment for the presence of induced abortion when estimating the rate of spontaneous abortion from cross-sectional studies. Am J Epidemiol 1983;117:305–8.
6. Figa-Talamanca I, Repetto F. Correcting spontaneous abortion rates for the presence of induced abortion. Am J Public Health 1988;78:40–2.
7. Hammerslough CR. Estimating the probability of spontaneous abortion in the presence of induced abortion and vice versa. Public Health Rep 1992;107:269–77.
8. Edmonds DK, Lindsay KS, Miller JF, et al. Early embryonic mortality in women. Fertil Steril 1982;38:447–53.
9. Whittaker PG, Taylor A, Lind T. Unsuspected pregnancy loss in healthy women. Lancet 1983;1:1126–7.
10. Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319:189–94.
11. Zinamon MJ, Clegg ED, Brown DD, et al. Estimates of human fertility and pregnancy loss. Fertil Steril 1996;65:503–9.
12. Bonde JP, Hjollund NH, Jensen TK, et al. A follow-up study of environmental and biologic determinants of fertility among 30 Danish first-pregnancy planners: design and methods. Reprod Toxicol 1998;12:19–27.

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THE FIRST TWO AUTHORS REPLY

The letter from Goldhaber and Fireman (1) nicely characterizes many of the complexities of estimating the number of spontaneous abortions, particularly in a situation in which induced abortion presents a significant competing risk. We also are pleased that they were able to confirm many of the assumptions we made in our study (2), especially that the estimated spontaneous abortion rates do not vary for women of different races.

Their letter (1) raises two important issues about spontaneous abortion rates. When comparing data from the Wilcox et al. study (3) (whose data we used to calculate our spontaneous abortion rates) and reanalyzing their Kaiser study data from 1981–1982 (4), Goldhaber and Fireman found differences in overall spontaneous abortion rates—16 percent for the Wilcox et al. study and 11 percent for the Kaiser reanalysis (1). The Kaiser study identified their cohort of women retrospectively through urine pregnancy tests or prenatal care registration at three clinics. While some pregnancies were identified as early as 5 weeks, the majority of women were not entered into the study until later in the pregnancy. Women who had pregnancy tests or spontaneous abortions outside the Kaiser system would not have been captured by their method. On the other hand, the longitudinal study reported by Wilcox et al. followed women prospectively, increasing the likelihood of identifying spontaneous abortions that occurred even outside the use of formal health care. Thus, we are not surprised by the difference in the reported spontaneous abortion rates and feel that the Wilcox et al. data more accurately reflect the actual rate.

Goldhaber and Fireman (1) suggest that we should have adjusted for the competing risk of induced abortions. When reviewing the methodological papers (5–7) for such adjustment, we encountered several approaches that included assumptions about the gestational age distribution of induced abortions compared with that of spontaneous abortions. Since we had limited information on induced abortions and the corresponding gestational distribution, we were not able to apply these methods. However, we discussed this issue in our paper (2) and acknowledged it as a limitation of our analysis. We agree with Goldhaber and Fireman that this is a difficult issue and that no consensus exists on how to correct for the competing risks of these two pregnancy outcomes.

References

1. Goldhaber MK, Fireman BH. Re: "Estimates of the annual number of clinically recognized pregnancies in the United States, 1981–1991." Am J Epidemiol 2000;152:287–8.
2. Saraiya M, Berg CJ, Shulman H, et al. Estimates of the annual number of clinically recognized pregnancies in the United States, 1981–1991. Am J Epidemiol 1999;149:1025–9.
3. Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. Am J Epidemiol 1981;114:548–53.
4. Goldhaber MK, Fireman BH. The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. Epidemiology 1991;2:33–9.
5. Susser E. Spontaneous abortion and induced abortion: an adjustment for the presence of induced abortion when estimating the rate of spontaneous abortion from cross-sectional studies. Am J Epidemiol 1983;117:305–8.
6. Figa-Talamanca I, Repetto F. Correcting spontaneous abortion rates for the presence of induced abortion. Am J Public Health 1988;78:40–2.
7. Hammerslough CR. Estimating the probability of spontaneous abortion in the presence of induced abortion and vice versa. Public Health Rep 1992;107:269–77.

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RE: "USE OF TWO-SEGMENTED LOGISTIC REGRESSION TO ESTIMATE CHANGE-POINTS IN EPIDEMIOLOGIC STUDIES"

Pastor and Guallar (1) have described an interesting problem in epidemiology, the use of two-segmented logistic regression. In the introduction to their paper, they stated that none of the usual methods provides inference procedures for estimating the location of the change-point. However, a method for estimating change-points was described several years ago (2). The situation considered there described a threshold with no effect below a certain level.

There has been much discussion about appropriate test statistics (3–6). More recently, an exact algorithm for estimating breakpoints in segmented generalized linear models was described (7). Finally, the results were compared by using different statistical models (8) that showed how the estimation can depend on the model used for the analysis. Careful modeling and interpretation seems to be very important.

When consequences are important, such as in the assessment of threshold values in occupational medicine, it is obvious that only one value is required. The work of Pastor and Guallar (1) is a first step, but a lot more must be done to enable this method to be used in practice.

Regarding the example used in the paper (1), several questions remain unanswered. How can a threshold be established? Is a formal test available? No value of any likelihood function (with and without a threshold) was given. What is the interpretation of a threshold or change-point if the corresponding parameter (β_2) is nonsignificant? In the example considered, it is unclear whether the parameters β_1 and β_2 are indeed significantly different from zero (table 2 (1)). In the paper, the authors compared five models that led to different estimates of the change-point. How can we discriminate between these models?

References

1. Pastor R, Guallar E. Use of two-segmented logistic regression to estimate change-points in epidemiologic studies. Am J Epidemiol 1998;148:631–42.
2. Ulm K. A statistical method for assessing a threshold in epidemiological studies. Stat Med 1991;10:341–9.
3. Cox C. Threshold dose-response models in toxicology. Biometrics 1987;43:511–23.
4. Ulm K. On the estimation of threshold values. (Letter). Biometrics 1989;45:1324–6.
5. Cox C. On the estimation of threshold values. (Letter). Biometrics 1989;45:1327–8.
6. Silvapulle JM. On testing for threshold values. (Letter). Biometrics 1991;47:1629.
7. Küchenhoff H. An exact algorithm for estimating breakpoints in segmented generalized linear models. Comput Stat 1997;12:235–47.
8. Küchenhoff H, Ulm K. Comparison of statistical methods for assessing threshold limiting values in occupational epidemiology. Comput Stat 1997;12:249–64.

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Editor's note: *In accordance with* Journal *policy, Drs. Pastor and Guallar were asked if they wished to respond to this letter but chose not to do so.*

RE: "DOES ARSENIC EXPOSURE INCREASE THE RISK FOR CIRCULATORY DISEASE?"

High levels of ingested inorganic arsenic in drinking water have been linked to arsenical dermatosis and to elevated risks of cancers of the skin, bladder, kidney, liver, and lung (1), as well as to diabetes mellitus (2, 3) and peripheral vascular and cardiovascular disease, but not cerebrovascular disease (4–6). Recently, Hertz-Picciotto et al. (7) observed that while high levels of arsenic in drinking water increase risk for a variety of diseases, most occupational studies of arsenic, in which inhalation is the primary route of exposure, have shown excess mortality only for respiratory cancer. This observation agrees with our summarization of 11 occupational studies of arsenic-exposed workers that showed consistent excesses only for respiratory cancer (8). Despite results to date, the hypothesis of a deleterious effect of inhaled arsenic for diseases other than respiratory cancer remains credible. Inhaled arsenic-containing dusts increase systemic arsenic, as demonstrated by elevated urinary arsenic in workers, to levels comparable with those found in populations consuming contaminated drinking water (9). Thus, one could posit that occupationally exposed cohorts should experience excess mortality for cancers of the kidney, bladder, and liver and for diseases of the circulatory system, particularly cardiovascular disease.

Hertz-Picciotto et al. (7) suggested that the absence of an excess mortality for circulatory diseases in occupational studies is due to a healthy worker survivor effect (HWSE), whereby exposure-related disorders result in early retirement or less hazardous jobs and, thus, in reduced total exposure. With data from a study of smelter workers in Tacoma, Washington, and adjustment for age and year of hire, there were no apparent arsenic-related trends in the relative risks for circulatory diseases, cardiovascular disease, or cerebrovascular disease. To account for the HWSE, the authors then added an adjustment for employment status (current or former worker) and determined exposures based on 10- and 20-year lag intervals. Although p values for tests of trend were not provided, there was a suggestive increase in the relative risk with arsenic exposure for circulatory diseases and for cardiovascular disease, but not for cerebrovascular disease. However, results were ambiguous, as there was no association between arsenic exposure and circulatory diseases using a G-null analysis (10), an alternative method for HWSE adjustment.

The paper by Hertz-Picciotto et al. (7) prompted a reexamination of our cohort of 8,014 Montana copper smelter workers (8). The study included all workers who were employed for 12 months or more prior to 1957, with follow-up starting on January 1, 1938, or 1 year after the start of employment and continuing through December 31, 1989. Because we had no information on exposures received after employment at the smelter ended, we restrict our analyses to person-years accrued by current workers and former workers last employed at age 50 years or older. A total of 6,885 workers contributed 120,900 person-years, with 1,615 deaths from all circulatory diseases (*International Classification of Diseases*, Eight Revision (11) (ICD-8) codes 390–459), including 1,115 deaths from cardiovascular disease (ICD-8 codes 410–414 and 420–429), 260 deaths from cerebrovascular disease (ICD-8 codes 430–438), and 45 deaths from peripheral vascular disease (ICD-8 codes 440–448). Exposure was expressed as years working in areas with heavy (mean, 11.3 mg/m^3), medium (mean, 0.58 mg/m^3), and light (mean, 0.29 mg/m^3) arsenic levels. Unspecified or unknown work areas were classified as work areas with light exposure. There were no indications of increasing risks with greater duration of exposure in work areas with light, medium, or heavy arsenic exposure, using the baseline model or after additional adjustment for the HWSE for cardiovascular disease (table 1) or for cerebrovascular disease (table 2). All tests of linear trends were not significant. Results for all circulatory diseases and peripheral vascular disease were similar (not shown). We also analyzed morality from diabetes mellitus (ICD-8 code 250), with 54 deaths and 27 deaths in the restricted data, and found no association with arsenic exposure.

The disease experience of former workers whose last employment at the smelter occurred before age 50 years was omitted in our analysis because there were sufficient cases only to analyze cardiovascular disease. There were no significant trends in the relative risks with the various measures of cumulative arsenic exposure. However, relative risks for 5–14, 15–24, and 25 years and more after cessation of employment were 0.80, 0.66, and 0.41, respectively, compared with 1–4 years after cessation of employment. These results do not suggest a relation between cardiovascular disease and cumulative arsenic exposure, but do suggest that cardiovascular disease "caused the retirement."

Along with most other occupational studies, we were unable to detect associations of inhaled arsenic with mortality from circulatory diseases or from cancer sites other than the respiratory tract. The more limited effect of inhaled arsenic stands in contrast to the excess of circulatory diseases and various cancers reported in populations exposed to arsenic-contaminated drinking water, despite equivalent levels of urinary arsenic. While an HWSE may indeed tend to obscure associations in occupational studies, the more systemic effects of ingested versus inhaled arsenic suggest different mechanisms of action that remain to be clarified.

References

1. Bates MN, Smith AH, Hopenhayn-Rich C. Arsenic ingestion and internal cancers: a review. Am J Epidemiol 1992;135:462–76.
2. Lai MK, Hsueh YM, Chen CJ, et al. Ingested inorganic arsenic and prevalence of diabetes mellitus. Am J Epidemiol 1994; 139:484–92.
3. Rahman M, Tondel M, Ahmad SA, et al. Diabetes mellitus associated with arsenic exposure in Bangladesh. Am J Epidemiol 1998;148:198–203.
4. Engel RR, Hopenhayn-Rich C, Receveur O, et al. Vascular effects of chronic arsenic exposure: a review. Epidemiol Rev 1994;16:184–209.
5. Wu MM, Kuo TL, Hwang YH, et al. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. Am J Epidemiol 1989;130: 1123–32.
6. Engel RR, Smith AH. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. Arch Environ Health 1994;49:418–27.
7. Hertz-Picciotto I, Arrighi HM, Hu SW. Does arsenic exposure increase the risk for circulatory disease? Am J Epidemiol 2000;151:174–81.
8. Lubin JH, Pottern LM, Stone BJ, et al. Respiratory cancer in a cohort of copper smelter workers: results from more than 50 years of follow-up. Am J Epidemiol 2000;151:554–65.
9. Hopenhayn-Rich C, Smith AH, Goeden HM. Human studies do not support the methylation threshold hypothesis for the toxicity of inorganic arsenic. Environ Res 1993;60:161–77.

TABLE 1. Relative risks and 95% confidence intervals for cardiovascular disease (ICD-8* codes 410–414 and 420–429), Montana, 1938–1989†

Years exposed	Length of exposure log interval (years)											
	Model‡: baseline						Model: baseline + work status					
	0		10		20		0		10		20	
	RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Light and unknown airborne arsenic work areas												
<5	1.0		1.00		1.00		1.00		1.00		1.00	
5–14	1.13	0.9, 1.4	1.07	0.9, 1.3	0.99	0.8, 1.2	1.21	1.0, 1.5	1.08	0.9, 1.3	0.98	0.8, 1.2
15–24	1.05	0.8, 1.3	1.08	0.9, 1.4	0.93	0.7, 1.2	1.16	0.9, 1.5	1.10	0.9, 1.4	0.92	0.7, 1.2
25–34	1.16	0.9, 1.5	1.06	0.8, 1.4	1.08	0.8, 1.5	1.35	1.0, 1.8	1.09	0.8, 1.5	1.07	0.8, 1.5
≥35	1.05	0.8, 1.4	1.43	1.0, 2.0	1.28	0.8, 2.0	1.26	0.9, 1.7	1.46	1.0, 2.1	1.27	0.8, 2.0
Medium airborne arsenic work areas												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1–3	1.08	0.9, 1.2	1.10	0.9, 1.3	1.18	1.0, 1.4	1.08	0.9, 1.2	1.10	0.9, 1.3	1.18	1.0, 1.4
4–7	0.86	0.6, 1.2	1.09	0.8, 1.5	1.04	0.8, 1.4	0.88	0.7, 1.2	1.09	0.8, 1.5	1.02	0.7, 1.4
≥8	1.05	0.8, 1.3	1.13	0.9, 1.5	0.88	0.7, 1.2	1.19	0.9, 1.5	1.15	0.9, 1.5	0.88	0.7, 1.2
Heavy airborne arsenic work areas												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1–3	1.02	0.8, 1.2	1.04	0.8, 1.3	1.02	0.8, 1.3	1.03	0.8, 1.3	1.04	0.8, 1.3	1.02	0.8, 1.3
4–7	0.93	0.5, 1.7	0.80	0.4, 1.6	0.69	0.3, 1.5	0.95	0.5, 1.7	0.80	0.4, 1.5	0.67	0.3, 1.4
≥8	1.25	0.9, 1.8	1.31	0.9, 1.9	1.07	0.7, 1.7	1.37	0.9, 2.0	1.31	0.9, 2.0	1.04	0.6, 1.7

* ICD-8, *International Classification of Diseases*, Eighth Revision; RR, relative risk; CI, confidence interval.

† Data restricted to current workers and former workers who were last exposed at age 50 years or more. No test of linear trend was rejected at the 0.05 level.

‡ Baseline model computes relative risks adjusted for age, year of follow-up, and age at first exposure. Work status is a time-dependent indicator variable denoting employment status.

TABLE 2. Relative risks and 95% confidence intervals for cerebrovascular disease (ICD-8* codes 430–438), Montana, 1938–1989†

Years exposed	Length of exposure log interval (years)											
	Model‡: baseline						Model: baseline + work status					
	0		10		20		0		10		20	
	RR*	95% CI*	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Light and unknown airborne arsenic work areas												
<5	1.00		1.00		1.00		1.00		1.00		1.00	
5–14	1.14	0.8, 1.7	0.99	0.7, 1.5	1.04	0.7, 1.5	1.23	0.8, 1.9	1.00	0.7, 1.5	1.05	0.7, 1.6
15–24	0.99	0.6, 1.6	1.00	0.6, 1.6	0.88	0.5, 1.5	1.10	0.7, 1.8	1.02	0.6, 1.7	0.90	0.5, 1.5
25–34	0.95	0.5, 1.6	0.71	0.4, 1.3	0.78	0.4, 1.5	1.12	0.6, 2.0	0.72	0.4, 1.3	0.78	0.4, 1.6
≥35	0.63	0.3, 1.1	0.70	0.4, 1.4	1.23	0.6, 2.7	0.77	0.4, 1.4	0.71	0.4, 1.4	1.25	0.6, 2.8
Medium airborne arsenic work areas												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1–3	0.95	0.7, 1.3	0.99	0.7, 1.4	0.76	0.5, 1.2	0.95	0.7, 1.3	0.99	0.7, 1.4	0.77	0.5, 1.2
4–7	1.12	0.6, 2.0	1.23	0.7, 2.2	1.39	0.8, 2.5	1.16	0.7, 2.1	1.24	0.7, 2.2	1.39	0.8, 2.5
≥8	0.84	0.5, 1.4	0.84	0.5, 1.4	1.10	0.6, 1.9	0.97	0.6, 1.6	0.86	0.5, 1.4	1.12	0.7, 1.9
Heavy airborne arsenic work areas												
0	1.00		1.00		1.00		1.00		1.00		1.00	
1–3	0.98	0.6, 1.5	0.87	0.5, 1.4	0.79	0.4, 1.4	0.97	0.6, 1.5	0.86	0.5, 1.4	0.77	0.4, 1.4
4–7	1.27	0.4, 4.1	1.27	0.4, 4.1	1.24	0.3, 5.1	1.30	0.4, 4.2	1.25	0.4, 4.0	1.25	0.3, 5.2
≥8	0.30	0.1, 1.3	0.35	0.1, 1.5	0.29	0.0, 2.2	0.33	0.1, 1.4	0.35	0.1. 1.5	0.28	0.1, 2.1

* ICD-8, *International Classification of Diseases*, Eighth Revision; RR, relative risk; CI, confidence interval.

† Data restricted to current workers and former workers who were last exposed at age 50 years or more. No test of linear trend was rejected at the 0.05 level.

‡ Baseline model computes relative risks adjusted for age, year of follow-up, and age at first exposure. Work status is a time-dependent indicator variable denoting employment status.

10. Robins J. A general approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. J Chronic Dis 1987;40 (Suppl. 2):139S– 61S.
11. International Agency for Research on Cancer. International classification of diseases. Adapted. USPHS publication no.1693. Washington, DC: US GPO, 1976.

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THE AUTHORS REPLY

In response to our recent paper (1) suggesting an association between circulatory disease mortality and occupational arsenic exposure that is seen only after adjustment for the healthy worker survivor effect, Lubin and Fraumeni (2) have reanalyzed data from the Anaconda smelter worker cohort. They are in agreement that there is biologic plausibility to this association, based largely on studies in populations with ingestion exposure, and despite their finding of no significant trend between duration of exposure and circulatory disease mortality, they and we believe that the data to date are not conclusive.

As discussed in an earlier paper (3), a complete adjustment for the differences in underlying health status between those who remain on a job and those who leave employment at that site is quite complex. The methods used by us and by Lubin and Fraumeni—lagging exposure and controlling for work status—provide only a partial adjustment. The problem is that any measure of cumulative exposure incurs the potential for this survivorship bias, since it is a function of length of employment. Nonetheless, the greater the association between the measure used and the duration of employment, the lower the chance of successfully controlling this bias through lagging and work status adjustment. Thus, it would have been more informative if Lubin and Fraumeni had compared different intensities of exposure among workers of similar duration rather than different durations among workers of similar intensity of exposure. From the results shown, no inferences can be drawn about intensity.

If there is an association between circulatory disease and some function of cumulative arsenic exposure, then the observed exposure response relation will reflect these two opposing phenomena: a declining risk with increasing length of employment due to the healthy worker survivor effect and an increasing risk with longer duration of employment due to greater accumulated exposure. In this circumstance, the healthy worker survivor effect can easily distort the dose-response relation, and therefore, even if exposure caused a linear increase in mortality, a nonlinear dose response might well be observed. For this reason, the test for linear trend would not be of interest (4). The results of Lubin and Fraumeni for cardiovascular disease (2, table 1) show consistent, although unstable, elevations in mortality relative risks among those with the longest durations of exposure in every analysis except that based on a 20-year lag among workers from medium airborne arsenic areas. Considering these observations and the lack of association with cerebrovascular disease, their findings are remarkably similar to ours.

Finally, the monotonically declining risk ratios for increasing years since leaving employment among workers who left the smelter prior to reaching age 50 years are interpreted by Lubin and Fraumeni as suggesting that cardiovascular disease "caused the retirement" (2, p. 000). This is an excellent description of how the healthy survivor effect operates; indeed, the findings seem to indicate that this bias also may not be well-controlled in the reported analysis for those who left employment at the smelter after age 50.

As previously discussed, G-estimation (5–7) provides the potential for a more complete and valid adjustment for the healthy worker effect without the problem of low statistical power that plagued our analysis based on the G-null test. We are currently conducting analyses on the Tacoma smelter worker cohort using G-estimation.

References

1. Hertz-Picciotto I, Arrighi HM, Hu SW. Does arsenic exposure increase the risk for circulatory disease? Am J Epidemiol 2000;151:174–81.
2. Lubin JH, Fraumeni JF. Re: "Does arsenic exposure increase the risk for circulatory disease?" Am J Epidemiol 2000;152: 290-3.
3. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. Epidemiology 1994;5:189–96.
4. MacClure M, Greenland S. Tests for trend and dose response: misinterpretations and alternatives. Am J Epidemiol 1992;135: 96–104.
5. Robins J. A new approach to causal inference in mortality studies with an sustained exposure period—application to control of the healthy worker survivor effect. Math Modeling 1986;7: 1393–512.
6. Robins JM, Blevins D, Ritter G, et al. G-Estimation of the effect of prophylaxis therapy for *Pneumocystis carinii* pneumonia (PCP) on the survival of AIDS patients. Epidemiology 1992;3:319–36.
7. Witteman JCM, D'Agostina RB, Stijnen T, et al. G-Estimation of causal effects: isolated systolic hypertension and cardiovascular death in the Framingham Heart Study. Am J Epidemiol 1998;148:390–401.

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